substitution, or addition of one or more amino acids to an active site of wild-type Factor IX or an active site of wild-type Factor IXa resulting in reduced ability to convert Factor X to Factor Xa.--

C1 cont

--~~36~~ 35. (amended) The method of claim ~~29~~ 1, wherein the recombinant mutein of Factor IX comprises at least one amino acid substitution from wild-type Factor IX sequence.--

C2

--~~40~~ 39. (amended) The method of claim ~~39~~ 6, wherein the substitution for Ser185 of wild-type Factor IXa is alanine.--

C3

REMARKS

Claims 1-40 are pending. Applicants have canceled claims 1-28, 31-32, 35, 37 and 38 without prejudice to applicants' right to pursue the subject matter of these claims in a future application. Claims 29, 36 and 40 have been amended to more particularly point out the claimed invention. The phrase "an active site of" has been inserted in claim 29. Support for this amendment may be found *inter alia* in the specification, on page 15, lines 9-14. Thus, claims 29, 30, 33-34, 36, 39-40 are pending and under examination.

Pursuant to 37 C.F.R. §1.121, a marked version of the amended claims showing all changes relative to the previous version of each amended claim is attached hereto as **Exhibit A**.

C

Claim Numbering

The Examiner stated that Applicant's amendments, mailed 4-7-00 and 6-16-00 (Paper No. 7 and Paper No. 10), are acknowledged. The Examiner stated that claim 29 has been amended. The Examiner stated that Applicant has added a new set of claims numbering 33-39. However, the Examiner stated that this newly added set of claims contains two claims which are numbered 36. So therefore, the Examiner stated that the last four claims originally numbered 36, 37, 38 and 39 have been renumbered 37, 38, 39, and 40, respectively. So, the Examiner stated that claims 33-40 have been added. The Examiner stated that claims 1-40 are pending, claims 1-28 and 31-32 have been withdrawn from consideration by the examiner as being drawn to the non-elected invention. The Examiner stated that claims 29-30 and 33-40 are being acted upon presently.

The Examiner acknowledged receipt of the Benedict et al. document.

Formal Drawings

The Examiner stated that the draftsman has reviewed the 26 sheets of formal drawings and a Notice of Draftperson's Patent Drawing review is attached to the instant office action.

Applicants will submit formal drawings upon the indication of allowable subject matter.

Sequence Listing

The Examiner stated that the application is in sequence compliance.

Status of Previous Rejections

The Examiner stated that the rejections of record can be found in the previous Office Action mailed 10-7-99 (Paper NO. 6). The Examiner stated that the 35 U.S.C. §112, second paragraph rejection and the Insley 35 U.S.C. §102(b) rejection are withdrawn. However, the Examiner stated that the Moller 35 U.S.C. §102(b) and §103(a) rejections are maintained as applied to newly amended claim 29 and its dependent claim 30.

Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner rejected claim 36 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that claim 36 is not supported by the specification or by the claims as originally filed. The Examiner stated that there is no support in the specification or claims as originally filed for the recitation "of a mutein of Factor IX with both limitations of 1) consisting of "essentially" of amino acids 1-47 of Factor IX and 2) further comprises at least one

amino acid substitution from wild type Factor IX sequence. The Examiner stated that with regard to the former limitation, the specification discloses on page 16, line 7, "only" in place of "essentially". The Examiner stated that "consists essentially of" is broader than "consists of ". The Examiner stated that there is no written description of the claimed invention in the specification or claims as originally filed. Thus, the Examiner stated that the claimed invention constitutes new matter.

In reply, applicants traverse the rejection. Without conceding the correctness of the Examiner's position, applicants have amended claim 36 to delete the phrase "consists essentially of" and to delete the first recited limitation in order to overcome the rejection. Applicants request that the Examiner reconsider and withdraw this ground of rejection in view of this amendment.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 29-30 and 33-40 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner stated that applicants' arguments, mailed 4-7-00 (Paper No. 7), have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action mailed 10-7-99 (Paper No. 6).

The Examiner stated that applicants assert that said claims are now enabled by their amendment to claim 29 which further characterizes the term "recombinant mutein" wherein the recombinant mutein comprises a substitution, deletion or addition of one or more amino acids to wild-type Factor IX or Factor IXa resulting in reduced ability to convert Factor X to Factor Xa. The Examiner took the position that this amendment still leaves an almost limitless number of muteins to consider. The Examiner stated that the specification provides guidance for making muteins of Factor IX which consist of amino acid substitutions of His221, Asp269 or Ser365, or muteins of Factor IXa which consist of amino acid substitutions of His41, Asp89 or Ser185. However, the Examiner stated that there is insufficient direction or guidance provided to assist one skilled in the art in the selection of <u>any</u> "proteolytically inactive recombinant muteins" that are effective for inhibiting clotting but do not significantly impair hemostasis, nor is there sufficient evidence provided that <u>any</u> such muteins are effective for inhibiting clotting but do not significantly impair hemostasis as recited in newly amended claim 29, for <u>any</u> recombinant mutein of Factor IX which consists essentially of amino acids 1-47 of Factor IX as recited in newly added claim 36, nor for <u>any</u> recombinant mutein of Factor IXa which comprises a deletion of one or more amino acids of wild type Factor IXa as recited in newly added claim 38. The Examiner stated that it would require undue experimentation to produce and investigate all such possible muteins without more explicit guidance from the disclosure. The Examiner stated that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the

method of inhibiting of clot formation in the subject which does not significantly interfere with hemostasis when said muteins, broadly encompassed by the claims, are added to the blood administered to a patient.

The Examiner stated that the working examples disclosed in the instant specification comprise only a minute fraction of the allegedly huge number of claimed embodiments, and the scope of the claims must bear a reasonable correlation with the scope of enablement.

The Examiner agrees with applicants' assertion that proteolytically inactive muteins Factor IX or Factor IXa where the recombinant mutein comprises a substitution, deletion or addition of one or more amino acid to wild type Factor IX or to factor IXa resulting in reduced ability to convert Factor X to factor Xa, are extensively described in the instant specification. The Examiner also agrees with applicants' assertion that murine models of human diseases are widely used. However, the Examiner noted that the working examples provided in the specification in the murine models were used in conjunction with chemical Factor IX which had been chemically modified by dansylation of the histidine of the active site, and there are no working examples of the above mentioned recombinant mutein. The Examiner further stated that although these mutations would likely destroy the active site of proteolysis, there is insufficient guidance from the specification to predict that said recombinant muteins would not significantly interfere with hemostasis. The Examiner took the position that the

predictability of which changes can be tolerated in a mutein's amino acid sequence and still retain the ability to inhibit clotting but not significantly impair hemostasis, allegedly requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the Examiner stated that the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Also, the Examiner stated that minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

The Examiner stated that minor structural differences among structurally related compounds or compositions, such as amino acid deletions of Factor IX and/or Factor IXa as recited in claims 35-38, such as amino acid substitutions in the active site of Factor IX comprising one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IX as recited in claims 33-34 and 36-37, or such as amino acid substitutions in the active site of Factor IXa comprising one or more of the following amino acids, His41, Asp89, and Ser185 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis. The Examiner stated

that given the lack of guidance concerning the nature of the modifications associated with muteins that the skilled artisan could use as a guide in making said muteins; it would require undue experimentation to practice the claimed invention.

So, the Examiner stated that due to the insufficient guidance in the instant specification regarding the effectiveness of the recombinant muteins, the insufficient working examples in animal models using recombinant muteins, and in view of the huge scope of the recombinant muteins, the invention as recited by claims 29-30 and 33-40 is not enabled.

The Examiner stated that applicants' arguments have not been found persuasive and the rejection is maintained as applied to newly amended claim 29 and its dependent claim 30, as well as to the newly added claims 33-40.

Applicants' Reply

In reply, applicants respectfully traverse the rejection and submit that one of skill in the art would be fully enabled to carry out the claimed invention in view of the disclosure combined with what one of skill would have known as of the effective filing date, i.e. September 27, 1996.

The claimed invention is directed to methods of inhibiting clot formation in a subject which comprises adding to blood an amount of an inactive recombinant mutein in an amount effective to inhibit clot formation in the subject but which does not

significantly interfere with hemostasis when the blood is administered to a patient, wherein the inactive recombinant mutein comprises: (a) a proteolytically inactive recombinant mutein of Factor IX, or (b) a proteolytically inactive recombinant mutein of Factor IXa and wherein the recombinant mutein comprises a substitution or addition of one or more amino acids to an active site of wild-type Factor IX or an active site of wild-type Factor IXa resulting in reduced ability to convert Factor X to Factor Xa.

The Examiner is concerned that the skilled person would be required to carry out undue experimentation in making and using the claimed invention because there are "a limitless number of muteins to consider." The claims have been amended and are now directed to methods using muteins which either have substitutions to amino acids in the active site or which have one or more additional amino acids in the active site which reduce or eliminate the ability of the protein to participate in the conversion of Factor X to Factor Xa.

The active site of Factor IX is a limited number of residues. It was known that three residues in particular confers the ability of the Factor IX or Factor IXa to convert Factor X to Factor Xa. The methods for creating muteins with a substitution of one or more of these three amino acid residues would have been known to one of skill in the art as of the effective filing date of the subject application. In addition, one of skill in the art would have known how to insert one or more amino acid residues within the active site of the Factor IX protein in order to

render it incapable of conversion of Factor X to Factor Xa. The synthesis or production of such Factor IX muteins would have been routine experimentation utilizing recombinant molecular biology techniques. Once such muteins had been created, one of skill in the art at the time of the effective filing date of the subject application, in view of the present disclosure, would have understood how to test the muteins for activity (it's ability to convert Factor X to Factor Xa). This assay is described in the present disclosure and would have been known to one of skill at that time. Therefore, applicants submit that one of skill in the art as of September 27, 1996, would have been able to make the Factor IX muteins recited in the claims (which include substitutions of amino acids or additions of one or more amino acids at the active site). Furthermore, one of skill in the art with the subject disclosure before them, would have known how to carry out an assay to determine if the previously synthesized mutein was capable of converting Factor X to Factor Xa. Therefore, applicants submit that one of skill in the art would have been fully enabled to carry out the claimed invention in view of what was known as of September 27, 1996, in combination with the subject disclosure.

In view of this discussion and the amendments herein, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claim 36 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the term "consisting essentially of" recited in claim 36 is a relative term which renders the claim indefinite because the specification has not stated what are the essential features of amino acids 1-47, and what are nonessential.

In reply, applicants traverse the rejection. Without conceding the correctness of the Examiner's position, claim 36 has been amended herein to delete the phrase "consisting essentially of" and to substitute therefor "comprising." In view of this amendment, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b) - Moller et al.

The Examiner rejected claims 29-30 and 33-36 and 38-40 under 35 U.S.C. §102(b) as being anticipated by Moller et al. (CA 2, 141, 642, in PTO-1449).

The Examiner stated that applicants assert that Moller et al. teach fragments of Factor IX, not muteins of Factor IX as recited in the instant claims. However, the Examiner stated that claim

29 recites muteins as encompassing deletions of Factor IX. The Examiner stated that a deletion of a full length wild type Factor IX at the carboxyl or amino terminals would produce a fragment of Factor IX. So therefore, the Examiner stated that the muteins recited in claim 29 and dependent claims 30, 33-35 and 38-40 encompass fragments of Factor IX which are taught by Moller et al. The Examiner stated that Moller et al. teach a Factor IXa mutein which does not show coagulation activity and does not significantly interfere with hemostasis as a method to treat ischemic events encompassed by the claimed methods (see entire document, including pages 1-2). The Examiner stated that the claimed functional limitations addressed by the applicants would be inherent properties of the referenced treatment of ischemic events associated with thrombotic disease using muteins (fragments) of Factors IX and IXa.

The Examiner agrees with the applicants that Moller et al. do not teach specific amino acid substitutions. However, the Examiner stated that the open language of the instant claims and the use of "essentially" in claim 36, requires the inclusion of claims 33-36 and 38-40 in the instant rejection.

In reply, applicants respectfully traverse the rejection. First, applicants point out that claim 36 has been amended to recite "consisting of" instead of "consisting essentially of." In addition, claims 29 and 37 have been amended to delete the term "deletion" and claims 35 and 38 have been canceled without prejudice. Therefore, the fragments of Factor IX and Factor IXa which are allegedly disclosed by Moller et al. are outside of the

scope of the claimed invention. In view of this amendment, applicants request the Examiner to reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §103 - Moller et al. in view of Brandstetter et al. and Insley et al.

The Examiner rejected claims 29-30 and 33-39 under 35 U.S.C. §103 as being unpatentable over Moller et al. (CA 2,141,642, in PTO-1449) in view of Brandstetter et al. (PNAS 92:9796-800, 1995) and Insley et al. (US Patent 4,711,848).

The Examiner stated that applicants argue that Brandstetter et al. only suggest the use of their X-ray structures of Factor IXa as a framework for localizing the interaction sites involved in Xase function. However, the Examiner points out that Brandstetter et al. teach that catalytic residues SER 365 and HIS 221 are in the active site of the serine protease (see entire document, especially page 9797, paragraph three) and also teaches in the last line of their article that this information can be used to make "testable predictions of sites suitable for mutagenesis experiments." The Examiner stated that inhibitory recombinant muteins of Factor IXa containing substitutions of said two residues were disclosed in the instant specification and recited in the newly added claims.

The Examiner stated that applicants assert that there is no motivation to combine Moller et al. and Brandstetter et al. However, the Examiner stated that that Moller et al. provide the

motivation of using muteins comprising fragments of Factor IXa to treat thrombotic diseases and thus an ischemic event that occurred as a result of said ischemic disease. The Examiner stated that Brandstetter et al. teach the active site of Factor IXa which encompasses several of the amino acid residue changes recited in the instant claims and provides even more motivation in the last line of the article which says that this information can be used to make testable predictions of sites suitable for mutagenesis experiments.

Therefore, the Examiner maintained the rejection as applied to newly amended claim 29 and its dependent claim 30.

The Examiner stated that the newly added claims 33-39 are drawn to method of inhibiting clot formation in a patient, which comprises adding an inactive recombinant mutein to inhibit clot formation but which does not significantly interfere with hemostasis.

The Examiner stated that Moller et al. teach the use of fragments of Factors IX and IXa, which do not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods (see entire document, including pages 1-2 and 20), but do not teach specific amino acid substitutions of Factors IX and IXa.

The Examiner stated that Brandstetter et al. teach the spatial distribution of variants of Factor IXa that have been identified in clinical studies in hemophiliacs, and in particular teaches

the catalytic residues SER365 and HIS221 that are in the active site of the serine protease (see entire document, especially page 9797, paragraph three).

The Examiner stated that Insley et al. teach methods of making site specific mutants of AT and that altered forms of AT that could be clinically important for use in inhibiting blood clotting, as for an example, in the treatment of disseminated intravascular coagulation, (entire article, especially column lines 30-40).

The Examiner stated that inhibitory recombinant muteins of Factor IXa of said two residues were referred to in the instant specification.

The Examiner stated that in order to accomplish a successful method of inhibiting clot formation in a subject using an inhibitory Factor IXa or Factor IX that does not significantly interfere with hemostasis, the ordinary artisan at the time the invention was made, would have been motivated to use an inhibitory Factor IXa or IX that does not significantly interfere with hemostasis as illustrated by the Factor IX and IXa fragments taught by Moller et al. and encompassed by the claims 33-36 and 38-39, which as discussed above encompass deletions and therefore fragments of Factors IX and IXa. The Examiner stated that for the same purpose, one also would have been motivated to use the mutations in Factor IXa found in hemophiliacs, and the knowledge of amino acids in the active site, and X-ray structure of Factor IXa as taught by Brandstetter et al., who, in particular teach

the catalytic residues Ser365 and HIS221, which are recited in claims 33 and 34, in order to make muteins containing specific amino acid substitutions in the active site as recited in claim 37, and/or deletions, as a substitute or as a modification for the inhibitory fragments of Factors IX and IXa taught by Moller et al., said mutations being produced according to the method of making recombinant mutants of Factor IX as taught by Insley et al., because Brandstetter et al. teach in the last paragraph of the article that this information by understanding of molecular mechanisms underlying hemophilia in which clot formation is inhibited, and that this information can be used to make testable predictions of sites suitable for mutagenesis, and thus one can transform a wild type Factor X or Factor IXa into a factor which inhibits clot formation.

The Examiner took the position that from the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the Examiner stated that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants' Reply

In reply, applicants respectfully traverse the rejection and maintain that the claimed invention is not rendered obvious by

the combination of Moller et al., Brandstetter et al., and Insley et al.

The claims are directed to, *inter alia*, methods of inhibiting clot formation in a subject which comprises adding to blood an amount of an inactive recombinant mutein in an amount effective to inhibit clot formation in the subject but which does not significantly interfere with hemostasis when the blood is administered to a patient, wherein the inactive recombinant mutein comprises: (a) a proteolytically inactive recombinant mutein of Factor IX, or (b) a proteolytically inactive recombinant mutein of Factor IXa and wherein the recombinant mutein comprises a substitution, or addition of one or more amino acids to an active site of wild-type Factor IX or an active site of wild-type Factor IXa resulting in reduced ability to convert Factor X to Factor Xa.

The applicable standard to determine obviousness is whether one of ordinary skill in the art as of the effective filing date, September 27, 1996, would have had <u>a reasonable expectation of success</u> for carrying out the claimed invention in view of the cited references. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991). The standard is <u>not</u> "obvious to try" and applicants submit that the Brandstetter et al. reference merely invites experimentation and does not provide a reasonable expectation of success when combined with the other two cited references. Specifically, the quotation pointed to by the Examiner, "testable predictions of sites suitable for mutagenesis

experiments" only invites the skilled person to experiment or to try. The "predictions" are "testable." "Mutagenesis *experiments*" are suggested. There is no reasonable expectation of success provided by Brandstetter et al., only a motivation to one of ordinary skill in the art to *try some experimentation* and this invitation *to try* does not make the claimed invention obvious. Applicants submit that the Examiner has not made a *prima facie* case as to the alleged obviousness of the claimed invention.

Clearly, it is well settled law that the "obvious to try" standard is not the standard to be applied in an obviousness analysis. See M.P.E.P. §2145 which states that

> [T]he admonition that 'obvious to try' is not the standard under §103 has been directed mainly at two kinds of error....In other [cases], what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as the particular form of the claimed invention or how to achieve it.

(Emphasis added and citations omitted.) *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). It is clear that the "obvious to try" standard set forth by the Examiner is improper and on this basis alone, applicants request that this rejection be withdrawn. Nevertheless, applicants will address the rejections as set forth by the Examiner under 35 U.S.C. §103 hereinbelow.

Brandstetter et al. provide structural information as to the x-ray structure of porcine factor IXaβ. An Xase model is disclosed

in Figure 4 is described as a "***starting point in understanding***...." Emphasis added. The authors state that "***aspects*** of this model ***might*** be transferable to related structures such as the prothrombinase complex." Emphasis added. See last paragraph of Brandstetter et al. Finally, applicants wish to put the phrase quoted by the Examiner into context. The authors state that the model in Figure 4 (a cartoon showing complex formation) "provides ***a framework*** for localizing the interaction sites involved in Xase function, making testable predictions of sites suitable for mutagenesis experiments." See Figure 4 and last paragraph of Brandstetter et al. This reference merely suggests exploration of a new approach, i.e. mutagenesis, and does not render obvious the claimed invention when combined with Moller et al. and Insley et al.

Moller et al. is cited to show the "use of fragments of Factors IX and IXa which do not show coagulation activity." See page 7, last paragraph of September 13, 2000 Office Action. Applicants have amended the claims to delete the term "deletion" so that the recombinant mutein comprises a substitution or addition of one or more amino acids. See amended claim 29. Since the claimed invention is no longer directed to deletions, i.e. fragments, the Moller et al. reference no longer applies. Therefore, the combination of Brandstetter et al. and Moller et al. will not make obvious the claimed invention, since the claimed invention no longer encompasses fragments of Factor IX or Factor IXa.

Insley et al. ("the '848 patent") teach methods for producing site-specific mutagenized alpha-1-antitrypsin. Applicants note

that the Examiner refers to lines 30-40, but does not specify a column, however, applicants believe the Examiner meant column 1. The '848 patent describes a single mutation in the gene sequence of alpha-1-antitrypsin which changes the normal function as an elastase inhibitor to that of a thrombin inhibitor. The '848 patent does not teach one of skill in the art methods of inhibiting clot formation without interfering with hemostasis using the recombinant muteins of Factor IX or Factor IXa as recited in claim 29.

Applicants submit that the combination of the cited references does not make obvious the claimed invention for the reasons stated hereinabove. In addition, there is no motivation to combine the '848 patent with either of the other two references. There is no mention of Factor IX or Factor IXa in the '848 patent. There is merely a statement regarding mutagenesis of an unrelated protein and this provides no motivation for one of skill in the art to combine the '848 patent with Brandstetter et al. or Moller et al.

In view of the amendments and discussion herein, applicants request the Examiner to reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $445.00 three-month extension of time fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M. Love

John P. White
Registration No. 28,678
Jane M. Love
Registration No. 42,812
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Jane M. Love 3/13/01
John P. White Date
Reg. No. 28,678
Jane M. Love
Reg. No. 42,812